Book Reviews

Current Developments in the Clinical Applications of HPLC, GC, and MS. Edited by A. M. Lawson, C. K. Lim, and W. Richmond. Academic Press, New York. 1980. xv + 301 pp. 23.5 × 15.8 cm. $51.50.

This book contains proceedings of the first of a series of international symposia organized by the Clinical Research Center, Middlesex, U.K., in 1979. Clinical applications of HPLC, GC, and MS are presented in 17 chapters. Seven chapters deal primarily with HPLC (soap chromatography, ion-pairing mechanisms, metabolic profiling of physiological fluids, bile pigments, peptides and proteins, plus a detailed discussion of combination HPLC–MS). Four chapters discuss the use of stable isotope-labeled compounds in biomedical applications (breath analysis and isotope dilution); one chapter notes that stable isotopes have unfulfilled potential in clinical research applications. Selected applications of clinical pharmacology are discussed in two chapters. Pyrolysis–MS of urine, bile, and fibroblast samples is described as a fast, first screening for metabolic disorders. GC–MS studies of organic acidurias and clinical steroid analysis are described in two chapters, while multicomponent analysis by capillary GC is described in another. Overall, the research described and reviewed by individual authors is of high quality. References are current to 1979. The aim of this book is timely: to survey the scope and limitations of HPLC, GC, and MS techniques and their application to clinical analysis. The editors are aware that clinical applications of most novel analytical instrumental developments appear much more slowly compared to chemical applications. This book is highly recommended to clinical analytical chemists and to researchers interested in those specific topics addressed in this volume.

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Drug Design. Volume X. Edited by E. J. Ariens.. Academic Press, New York. 1980. 16 × 23.5 cm. XI + 426 pp. $49.50.

Volume X is a continuation of the "Drug Design" series, which, for a decade, has brought to a selected audience chapter-length insights into various facets of product-oriented medicinal chemistry. This volume continues that tradition with a mix of articles ranging from theoretical SAR treatments to a consideration of polymers. The authors are equally divided in their affiliation between industry and academe. The selection of topics follows no particular pattern; as a result, this volume and the more recent volumes resembles an annual review rather than a primer or text.

The first chapter by Austel and Kutter is a very scholarly and well-written treatment of the theory of sets applied to drug design. The second chapter by the Janssen group examines SAR from the standpoint of conformation prediction and analysis. Emphasis is on X-ray studies and MO calculations, unfortunately using only one semiempirical method. The pharmacological focus is on neuroleptic agents.

Chapter 3 is an interesting and valuable review by Farmer on the design of peptide–nonpeptide hybrid molecules as analogues of bioactive peptides. Struyker–Boudier describes rather briefly the systems analysis application to hypertensive drug action in Chapter 4.

The next two chapters on "Polymeric Drug Delivery Systems" and on "Design of Biocompatible Polymers" are useful and timely, offering some insight and, hopefully, stimulus in this area. Chapter 7 on "Insect Repellents" by Skinner and Johnson brings the interested reader up-to-date in this area of vital importance to scientists working on environmental problems.

In Chapter 8, Lewi attempts to bring some order into the emerging use of multivariate data analysis. The final chapter by Mager is a continuation of the description of the Masca model, which was introduced in the previous volume of this series. It is unfortunate that the editors did not put this topic in contiguous chapters in a single volume.

The cost of this volume reflects the general rise in production expense in recent years but still makes the purchases of individual copies recommended for readers who are interested in several topics within the volume. It is certainly desirable to have this volume as a library holding in industries and universities where there is any patronage by medicinal chemists.

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Angiotensin Converting Enzyme Inhibitors. Mechanisms of Action and Clinical Implications. Edited by Z. P. Horovitz. Urban and Schwarzenberg, Baltimore. 1981. xv + 451 pp. 16 × 24 cm. $35.00.

This text consists of the Proceedings of the A. N. Richards Symposium which was sponsored by the Physiological Society of Philadelphia and held May 8–9, 1980. The papers which were contributed by some of the leading authorities of the renin–angiotensin system have been divided into several sections. The first section details the development of the converting enzyme inhibitors teprotide and captopril and the effect that these agents have on the various animal models of hypertension and on the brain. The papers in Section Two discuss the mechanism of action of converting enzyme inhibitors. The primary focus of this section is the relationship between the kallikrein–kinin system and angiotensin converting enzyme and the possible role that this relationship may play in the antihypertensive effects of converting enzyme inhibitors. In Section Three the effects that captopril has on fluid balance and other hemodynamic parameters are addressed, while in Section Four the papers described some of the clinical pharmacological studies which have been carried out with captopril. Section Five contains the A. N. Richards Memorial Lecture which was presented by John Laragh. Dr. Laragh provides an excellent review of the renin–angiotensin system and its relationship and involvement in hypertension.

The papers are, by and large, well written. The individual authors make extensive use of tables, graphs, and diagrams to illustrate the points they are trying to make. References are provided for each paper, and although they are not exhaustive, they do represent many of the key references in the area. The discussions which were held by the participants of the symposium have been included after each section, and a subject index is provided. Investigators working in the areas of the renin–angiotensin system and hypertension will certainly find this book useful.

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Heterocyclic Chemistry. Volume 1. Specialist Periodical Reports. Edited by H. Suschitzky and O. Meth-Cohn. The Royal Society of Chemistry, Burlington House, London. 1980. xx + 522 pp. 13.5 × 21.5 cm. $186.50.

This book is the first of a new series which will survey, on an annual basis, the chemical literature in the field of heterocyclic chemistry. The first volume reviews the period from July 1978 to July 1979. It covers the full spectrum of heterocyclic chemistry from oxirans to fused unsaturated systems.

The text contains eight chapters which are organized by ring size and the type of heteroatom(s) contained within them.

Chapters 1 through 7 deal mainly with the synthetic aspects of heterocycles, while chapter 8 provides an interesting report on conformational analysis studies conducted on a variety of ring systems. Chapters 2 and 3 cover five- and six-membered ring systems, respectively, and are divided into several parts in order to examine the voluminous research that appeared on these systems during the period of time of the review. Other than chapter 8, each chapter or part provides a blend of synthetic methods, probable reaction mechanisms, and spectroscopic information. All contributors direct the reader to current reviews on their topics. They provide detailed references to the material covered, and these references conveniently appear at the bottom of each page. An author index is also provided.

This series should become an extremely valuable resource for those academicians involved in the teaching and synthesis of heterocycles, as well as for those heterocyclic chemists in an industrial setting. Although the price ($186.50) may be prohibitive for inclusion in personal collections, it should be a useful addition to institutional libraries.

The editors are to be complimented for their excellent choice of contributors and for the skillful organization of the text material.

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Topics in Enzyme and Fermentation Biotechnology. Volume 5. Edited by Alan Wiseman. Halsted Press (A Division of Wiley), New York. 1981. 359 pp. 16 × 23.5 cm. $89.95.

This continuation volume of "Topics in Enzyme and Fermentation Biotechnology" is a multiauthored text assembled by Editor Alan Wiseman. As with previous members of this series, it includes a wide range of subjects relating to fermentation and biotechnology. The book takes essentially the same format as previous volumes, and it is aimed toward people engaged in research in microbiology, biochemistry, chemistry, and biochemical engineering. Indeed, topics should be of interest to individuals in the food, brewing, textile, and pharmaceutical industries. The book begins with a brief introductory chapter (2 pages) by the editor in which he sets the tone for the diverse chapters which follow.

Chapter 2 covers the topic of immobilized coenzymes in great detail in some 134 pages containing more than 200 literature citations, most of which date earlier than 1979. The subject is presented authoritatively by C. Lowe, and it ranges from a description of the interactions of various coenzymes, such as NAD and NADP with complementary enzymes, to the chemical synthesis of defined coenzyme analogues. Problems encountered in characterizing coenzyme analogues and especially those attached to immobilizing matrices are well-covered. The exploitation and application of immobilized adenine coenzymes in enzyme purifications, resolutions of isoenzymes, and purification of mutant proteins are described. This chapter is very well-written and illustrated, and it honestly protrays the difficulties and successes of this developing field.

Chapter 3 is an assay by J. Darbyshire dealing with the subject of large-scale enzyme extraction and recovery, and the topic is presented in 40 pages with 60 literature citations, most of which are pre-1980. Basic principles involved in large-scale enzyme isolations are covered (i.e., greater than 1 kg of cell paste or 20 L of medium), and attention is directed away from laboratory scale procedures which have been covered elsewhere. Problems encountered with extracellular enzymes which must be concentrated and intracellular enzymes requiring methods for cell disruption are covered. This chapter is less detailed than others in the text.

E. Vandamme presented a clear and detailed discussion of the properties, biogenesis, and fermentation of the cyclic decapeptide antibiotic gramicidin S. This wide-ranging chapter covers 74 pages with some 247 references, most of which are dated 1980 or earlier. It begins with a review of cyclic peptide and oligopeptide antibiotics and then covers aspects of the isolation, structure, and chemical and antimicrobial properties of gramicidin S. The mode of action, structure–activity relationships, and uses of gramicidin S are also reviewed. The biosynthesis of gramidicidin S involving the so-called protein-thiotemplate mechanism is described in well-illustrated detail. Problems encountered with the gramicidin S fermentation were also discussed, including the results of nutritional studies and fermentation optimization experiments. The chapter is a very comprehensive coverage of the field.

Chapter 5 by K. Brocklehurst, B. S. Baines, and M. P. J. Kierston is devoted to the subject of papain and other constituents of *Carica papaya* L. (64 pages and 274 references, most of which are pre-1980). The latex of *C. papaya* L. contains several enzymes, including papain, propain, chymopapains A & B, papaya peptidase A, and papaya lysozyme. The methods involved in the production of the latex and in the production of papain are covered, and considerable attention is given to studies designed to alter thiol and imidazole functional groups of cysteine and histidine residues of papain and to the activities of altered enzymes. Applications of papain in brewing, in meat, fish, and other foodstuffs, and in the pharmaceutical industries are also presented.

The sixth and final chapter is an essay by Editor Wiseman discussing alcohol dehydrogenases, their immobilization and applications. The chapter is less detailed than others in the text, covering some 25 pages with 90 literature citations. The wide variety and occurrence of alcohol dehydrogenases are cited, and applications of free and immobilized enzymes as analytical tools are illustrated. The stereospecificities of various alcohol dehydrogenases render them attractive for applications in synthetic organic chemistry.

In general, the chapters are authoritatively presented by individuals who have worked in the areas covered. The information contained in these chapters should serve as an excellent resource for those currently active in the fields and for those with more casual interests.

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Advances in Substance Abuse. Volume 1. Behavioral and Biological Research. Edited by Nancy K. Mello. Aijai Press Inc., Greenwich, CT. 1980. vii + 376 pp. 15.5 × 23.5 cm. $37.50.

This volume is the first of a new series of collections of reviews of substance abuse. The closest existing series of such reviews is the *Research Advances in Alcohol and Drug Problems* edited by members of the Addiction Research Foundation, Toronto, and published by Wiley. Since this field has so many ramifications, neither series is likely to duplicate what the other has done, but rather they will be complementary.

The present volume consists of eight reviews, some by authors who are well known in the field and others by apparent newcomers. Griffiths, Bigelow, and Henningfield review the evidence supporting the idea that although important differences exist between self-administration of different drugs, both in animals and man, at least in man drug self-administration variables exert an independent influence. Impressive similarities can be found between the animal experimental work, human experimental work, and clinical information on drug taking. Gritz, who is associated with Murray Jarvik, reviews the work on the factors that reinforce smoking behavior and offers some suggestions concerning treatment of tobacco abuse. Marlatt and Rohsenow take a rather controversial stance in discussing cognitive processes in alcohol use. Using a balanced placebo design that might not be able to pass current ethical standards, they conclude that expectation of what alcohol may do may be more important than the pharmacological effects of the drug itself in reinforcing its use. Most people are not yet willing to accept the notion of alcohol as an active placebo. Cicero reviews authoritatively the effects of alcohol and narcotics on the endocrine system. Some of the findings may explain clinical phenomena associated with the use of those drugs. Bernstein, associated with the Mendelson–Mello group reviews the medical consequences of marijuana use, as well as the therapeutic potential for the drug. A trio from the National Institute of Drug Abuse, Stillman, Barnett and Petersen, consider the epidemiology, pharmacology, and pharmacokinetics of phency-

clidine (PCP). At the time of their writing, the problem loomed large, but recent trends toward diminished use of this potentially dangerous drug have been encouraging. No one can write with more authority than Donald Goodwin on genetic factors in alcoholism. He suggests that one might best think of two types of alcoholism, familial and nonfamilial. Randall and Noble (the latter is the former director of the National Institute on Alcohol Abuse and Alcoholism) review current knowledge about the fetal alcohol syndrome. Safe levels of drinking during pregnancy are unknown, but definite risk is established with ingestion of more than 90 mL of absolute alcohol (or six drinks) per day.

Anyone who has tried to solicit review articles knows how very difficult it is to get persons who are knowledgeable in a field to take time from their original investigations to write reviews. Yet authoritative reviews are extremely helpful, sometimes I suspect as much to the reviewers as to their audience. This new series is a welcome addition in the field of substance abuse and will help to make sense of the growing literature on the subject. The first volume provides a most auspicious start for the series.

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Chemistry of Heterocyclic Compounds. Volume 40. Parts 1 and 2. Benzimidazoles and Congeneric Tricyclic Compounds. By P. N. Preston, M. F. G. Stevens, and G. Tennant. Edited by A. Weissberger and E. C. Taylor. Wiley-Interscience, New York. 1981. Part 1: x + 687 pp. 15.5 × 23.5 cm. $175.00. Part 2: x + 581 pp. 15.5 × 23.5 cm. $175.00.

This volume continues the subject matter of the sixth volume (authored by Klaus Hofmann in 1953) of this series.

The volume is divided into two equal five-chapter parts. Chapters 1–3 are concerned with benzimidazoles, benzimidazole *N*-oxides, and dihydro derivatives; chapters 4–8 describe various condensed benzimidazoles in terms of the position and size of the ring fused to the benzimidazole skeleton; chapter 9 surveys condensed benzimidazoles bridged between N-1 and C-7; and chapter 10 is a compilation of commercially marketed benzimidazoles.

Each of the chapters is preceded with an outline; the body of the chapter is divided with bold, centered subtitles; systematic tabular surveys for each class of benzimidazole described and references for the chapter material conclude each chapter. The references survey the literature through Volume 87 (1977) of Chemical Abstracts. Numerous structural drawings are clearly related by numbers to the textual material. Both parts end with author and subject indexes.

The volume is well done, maintaining the high standards of all books of this useful series, and should certainly be available to all those concerned with the various facets of imidazole chemistry.

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Advances in Cancer Research. Volume 33. Edited by George Klein and Sidney Weinhouse. Academic Press, New York, London, Toronto, Sidney, and San Francisco. 1980. vii + 325 pp. 15 × 23 cm. $37.50.

This rapidly growing series of volumes containing many excellent, highly informative, in-depth reviews on a variety of timely topics relating to cancer research has always been most representative in the areas of tumor biology and immunology. However, many of the earlier volumes also contained treatises that were more biochemical or pharmacological in nature than those in the present volume. The first article in this volume reviews the nature, advantages, and application of the chemostat (continuous flow) culture for the study of tumor cell multiplication. One application of this system, in studies of the mode of action of interferon, is discussed in more detail. The second review deals with the nature and possible mechanism of production of the so-called ectopic hormones, i.e., several known peptide hormones produced in tumors. The third and fourth chapters are in the areas of viral oncology; the former, by H. Z. Hausen, reviews current information relating to the role of viruses in human tumors, while the latter, by P. Andersson, discusses at some length the oncogenic function of mammalian sarcoma viruses, particularly from the point of view of genetics. The fifth chapter by Mingxin et al. describes recent progress in the epidemiology, etiology, diagnosis, treatment, and prevention of esophageal cancer in China. The sixth and final chapter, under the title "Mass Transport in Tumors", by Jain et al., presents various pharmacokinetic models and considerations that may be helpful in the understanding of the quantitative aspects of drug transport in the chemotherapy of solid tumors. Each of these reviews is expertly written, up-to-date, and well referenced. Therefore, this book is of particular value to those scientists who are interested in obtaining detailed information on any of the above-mentioned special topics.

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Annual Reviews Reprints: Cell Membranes, 1978–1980. Compiled by L. J. Mullins. Annual Reviews, Inc., Palo Alto, CA. 1981. viii + 889 pp. 15.5 × 23 cm. $28.00.

The first volume of this series ("Annual Reviews Reprints: Cell Membranes, 1975–1977") was an experiment to see if the scientific community would find useful a compilation of reviews on a *topic* as distinct from a *discipline*. The reception accorded this first volume was such as to encourage the compilation of the present volume of reviews covering the years 1978, 1979, and 1980. The number of articles published in all Annual Reviews in the field of cell membranes has more than doubled—clearly the editors and editorial committees of a variety of *Reviews* all are finding that the field of cell membranes impinges on their disciplines. A new section has been added on cell membrane receptors, since this is a rapidly developing area of research.

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Toxicants and Drugs: Kinetics and Dynamics. By Ellen J. O'Flaherty. Wiley, New York. 1981. xvi + 398 pp. 17 × 24 cm. $42.50.

The word "toxicants" should catch the reader's eye with anticipation that pharmacodynamic problems of toxicologic interest will be emphasized in this book. The author's background in environmental health indeed helps to lend such an emphasis. This material serves well to bring kinetic principles to an introductory course in toxicology.

The first chapter is a useful review of the simple algebraic and calculus techniques required for manipulation of kinetic equations. However, some confusion exists regarding independent and dependent variables in the very first table, and few derivations were made in subsequent chapters to put the calculus techniques into practice. Chapter Two considers the kinetics of saturable systems. While kinetic and graphical principles related to capacity-limited processes and metabolic inhibition are often treated, this presentation is lucud and well-embodied with actual experimental data culled from numerous literature sources. Here, also, the author begins a lauditory practice of providing several pages of homework problems, most of which are literature examples to which kinetic principles can be realistically applied. This direct application of kinetic and graphical principles to an extensive array of actual experimental data is one of the highlights of this book.

Chapter Three is entitled "Acute Exposure with First-Order Disposition". This serves as a familiar but essential review of first-order processes, diffusion across biological membranes, and the one and two compartment body models. Classical compartmental models are presented well, but a major deficiency is the absence of flow–organ clearance models of drug disposition, and the first-pass effect is barely mentioned. Nonlinear and mixed kinetics of disposition are handled in Chapter Four. The major sources of nonlinearity related to protein binding, biotransformation, renal excretion, and alteration of blood flow are described, and many typical examples from the literature are provided both

in the text and problem set. The kinetic consequences of chronic exposure are provided in Chapter Five with description of the plateau principle and steady-state accumulation in a multiple compartment model as central features. The chapter ends with a useful demonstration of practical uses of the plateau principle with clinical, experimental, industrial, and toxicological applications briefly provided.

The final third of the book deals with pharmacodynamics, and Chapter Six begins with dose–effect relationships, receptor theory, and the role of various types of antagonists. It provides an instructive blend of basic concepts and equations with an extensive array of detailed examples mostly dealing with enzyme or tissue systems. The time course of in vivo drug effect is considered in Chapter Seven. Temporal effect measurements are treated as they relate to drug concentration in plasma, dose, and the kinetics of drug disposition. Most of the material is that developed by Gerhard Levy. The final chapter is entitled "Dose Response Relationships" and differs from the previous sections by addressing the population response to drugs or toxicants. Included are graphical analyses such as the probit plot, joint action of effectors, the relationship of length of exposure to response, and extrapolation of response measurements to very low exposure levels. Most of the examples depict environmental contaminants in a fitting and instructive manner.

The extensive list of references and array of graphical examples of drug and toxicant kinetics will make this book both a useful teaching and research source. Graduate and advanced undergraduate students in pharmacology, toxicology, or industrial medicine will find this an excellent base for a semester's course in pharmacodynamics. The mathematics are limited in complexity, and the emphasis is clearly on explanation and application of basic kinetic principles. The author's expertise as a teacher illuminates most of the pages.

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Pharmacokinetics. Edited by E. Gladtke and G. Heimann. Gustav Fischer Verlag, Stuttgart and New York (Distributor: Verlag Chemie Int., Deerfield Beach, FL). 1980. 276 pp. 17 × 24 cm. $47.50.

This book is a collection of all the papers presented before the International Pharmacokinetics Symposium held in Cologne, West Germany, in November of 1978. The book started with Dettli's chronological overview of the progress in pharmacokinetics during the past 25 years. For the convenience of reviewing, I will divide the subjects into six groups.

Group 1: Pharmacokinetic Modeling. Rupp (p 151) reviewed practically all computer programs which have been used in pharmacokinetic analysis. Hattingberg and Brockmeier (p 165) and Sereni et al. (p 201) both demonstrated the use and value of computers in pharmacokinetic analysis and in therapeutics. Van Rossum and Van Ginneken (p 53) compared different functions and various models for pharmacokinetic analysis. A physiological model was proposed and tested on the receptor binding of estradiol. While others may fail to agree to the authors' statement that "a direct relationship between plasma concentration and effect is likely an utopia and a waste to persue it" (p 72), systems dynamics is certainly a powerful approach to the elucidation of pharmacological action.

Group 2: Pharmacokinetics and Dosage Regimens. Follath et al. (p 109) discussed the deficiency of a one-compartment model. Riegelman et al. (p 83) undertook a sophisticated, population-based approach to the assessment of mean values for pharmacokinetic parameters. A nonlinear mixed effect model was proposed for this purpose. Jusko (p 181) applied a traditional multiregression analysis to assessing the mean clearance of theophylline. In contrast, Ritschel and Thompson (p 141) advocated an intrasubject approach by giving a "test-dose" followed by a "one-point" or "repeated one-point" kinetic study. Provided that (1) the ethics of a "test dose" are acceptable to clinicians and patients and (2) the availability of laboratory data before the next dosing is not in question, these methods may work out as hoped. Eventually, the patient data generated from these monitoring methods should be pooled into the population pharmacokinetics for better utilization.

Group 3: Pharmacokinetic Analysis of Efficacy and Toxicity. Garrett (p 23) and Galeazzi (p 225) both gave a brief, but clear, review of the mathematical procedures used in the analysis of dose–response relationships. Garrett, Uehleke (p 261), and Oesch (p 75) further discussed the pharmacokinetics of toxic response. Although heavier weight was carried on the discussion of therapeutic response rather than toxic effect, readers will find useful references from these articles for further persuing of this subject.

Group 4: Factors Which Affect Drug Absorption. Weber and Gundert-Remy (p 97) and Leopold et al. (p 117) discussed factors which potentially affect the outcome of a bioavailability testing. Heimann (p 211) discussed the age dependence of drug absorption in children. Most of these factors are well-known and are reemphasized in a well-organized manner. Dengler et al. (p 7) used D_3-verapamil to demonstrate bioavailability studies in which the reference standard was administered simultaneously with the test dosage form, avoiding the possible changes of biological conditions which could occur to the test subjects had the studies been performed traditionally.

Group 5: Factors Which Affect Drug Disposition. Hepatic function is crucial in determining drug kinetics. The effects were clearly demonstrated by Klotz's (p 243) work on a few drugs administered in the liver disease state. Liver function tests are discussed by Klotz as well as by Jäger et al. (p 271). Dengler et al. (p 7) used [^{15}N]carbamazepine to investigate the effects of chronic treatment, disease state, and combined therapy on the metabolism of carbamazepine without interupting the treatment regimen. Coupled with their presentation on D_3-verapamil absorption, Dengler et al. very effectively demonstrated the use of isotopes in pharmacokinetic reserach. Klinger (p 191) discussed the proceeding of maturity on drug biotransformation; however, his discussion of "flow-limited" and "supply-limited" elimination was somewhat confusing. Van Kobyletzki (p 253) discussed the effect of pregnancy on transplacental distribution and drug passage into the milk. Barber (p 235) very nicely summarized the effects of protein binding on half-life, steady-state concentration, and pharmacological action.

Group 6: Pharmacokinetics and Drug Design. As in QSAR, a multiregression analysis was employed by Seydel (p 39) to correlate the pharmacokinetic parameters and the physicochemical properties for a series of sulfonamides. The significance of this correlation should lead to a rational approach in the development of drugs with certain desirable pharmacokinetic characteristics.

In summary, I can recommend this book as a reference text to graduate students or researchers in the pharmacokinetics area. However, I feel sorry to see it contaminated with many typographical errors, a misprinted equation (eq 3, p 30), a poorly arranged equation (eq 9, p 147), a missing symbol (Figure 2, p 28), a missing figure (Figure 8, p 71), and a missing table (Table 4, p 71). The inconsistent notations throughout the book make it of little value to beginner and layman.

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Molecular Actions and Targets for Cancer Chemotherapeutic Agents. Bristol-Myers Cancer Symposia. Volume 2. Edited by A. C. Sartorelli, J. S. Lazo, and J. R. Bertino. Academic Press, New York. 1981. xxvi + 598 pp. 16 × 23.5 cm. $45.00.

This book contains the proceedings of the Second Annual Bristol-Myers Symposium on Cancer Research, organized by the Yale University Department of Pharmacology and the Developmental Therapeutics Program of the Comprehensive Cancer Center, and held November 8–9, 1979. The biggest fault to be found with the book is the length of time between its publication and the meeting. Much, if not all, of the new material has already been published in journals, detracting from the impact of this volume.

The book is divided into seven parts: "Alkylating Agents", "Antibiotics", "Antimetabolites—Nucleoside Analogs", "Antimetabolites—Folate Analogs", "Radiation Sensitizers",

"Membrane Targets", and "Angiogenesis–Metastasis–Anticarcinogenesis–Differentiation", corresponding to the meeting sessions. The chapters, two to five in each part, are short ranging from 9 to 35 pages. Most aspects of cancer chemotherapy are covered from the cross-linking of DNA to the transport of nucleosides and folate analogues to radiation sensitizers. In addition to the topic of conventional chemotherapy, newer areas potentially useful in cancer control, such as angiogenesis inhibitors, the effect retinoids have in preventing cancers and metastatic growth, and differentiation and its induction, are covered. Although some of the topics are well worn with up-to-date reviews by the same authors having appeared in several other collections, some, such as 5′-(methylthio)adenosine as a target of chemotherapy, were novel at the time of the meeting and still have received only limited coverage. Even one well acquainted with cancer chemotherapy will benefit from reading parts of this collection, if not the whole volume. Although it may present the uninitiated with an uneven view of the status of the field today, it nonetheless can serve as a reasonable, if somewhat esoteric, introduction to cancer treatment.

A major omission of the meeting, and the book, is coverage of purines in Part III ("Antimetabolites—Nucleosides"). Thus, although two chapters discuss analogues of 5′-(methylthio)-adenosine that may eventually be of interest in cancer treatment, there is no coverage of the useful 6-thiopurines. Despite the utility and interest in arabinonucleosides, they are not discussed either. On the other hand, two chapters are devoted to 5-fluorouracil, and Part IV (four chapters) is devoted entirely to methotrexate and related compounds. I could find no mention of cyclophosphamide in the chapters devoted to alkylating agents. The coverage undoubtedly reflects the bias of the organizers and probably their assessment of new developments in studies of the various drug types at the experimental level at the time the meeting was planned.

The book itself is of high quality in all respects and relatively error free.

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Advances in Polyamine Research. Volume 3. Edited by Claudio M. Caldarera, Vincenzo Zappia, and Uriel Bachrach. Raven Press, New York. 1981. xvii + 478 + 15 pp. 18 × 26 cm. $55.00.

The third volume [vol. 1 was reviewed in *J. Med. Chem.*, 21, 1184 (1978)] in this series represents 42 papers presented at a Symposium sponsored by the Italian Biochemical Society and the University of Bologna that was held at Rimini, Italy, in September 1980. The editors state that in excess of 1500 papers were published in this field during the last decade, an indication of the intense research effort being directed toward the elucidation of the many unknown properties of that class of compounds.

The polyamines, principally the dications putrescine, spermidine, and spermine, are ubiquitous intra- and extracellular substances present in millimolar concentrations in all living systems. They perform a complex variety of biological functions. As strong bases, they can substitute for the cations K^+ and Mg^{2+}. Even more importantly, they are capable of covalently bridging strands of double-helical nucleic acids and can, as a consequence, regulate nucleic acid and protein synthesis.

The four-carbon putrescine is formed most simply by decarboxylation of ornithine; that process is induced by the enzyme, ornithine decarboxylase (ODC), but controlled via a biofeedback mechanism that involves a specific enzyme inhibitor, ODC–antizyme. This area of research, including efforts to obtain the crystalline antizyme, is represented by seven papers. Decarboxylation of *S*-adenosylmethionine, followed by transfer of the liberated aminopropyl group to one of the nitrogen atoms of putrescine by spermidine synthase (SS), leads to the seven-carbon spermidine. Investigations into that process and attempts to purify SS are discussed in two papers. The metabolism of these biologically active polyamines by mono- and diamine oxidases is described in two papers.

Aside from a number of chapters which demonstrate the presence of these polyamines in amniotic fluid, human semen, heart cells, plants, bacteria, and protozoa, the major thrust (20 papers) of the symposium was to elaborate the role of ODC inhibitors. That group of compounds presently include α,α-bis(fluoromethyl)ornithine (α-DFMO), α-methylornithine (α-MO), methylglyoxal bis(guanylhydrazone) (MGBG), and methylglyoxal bis(aminoguanylhydrazone) (MBAG). More recently, interferon has been shown to be a specific inhibitor of both ODC and SS. Although the mechanisms of these inhibitions are not understood, the logical development, since neoplastic cells contain higher intracellular concentrations of polyamines than normal cells, has been to study these inhibitors in the treatment of malignant brain and testicular tumors. Thus far, unfortunately, both animal and human studies have revealed slight activity only in medulloblastoma. One aspect of these investigations that may have promise for the future lies in the demonstration of a symbiotic effect; namely, that the administration of an active anticancer drug in combination with an ODC inhibitor achieves a clinical response that is greater than that obtained with either drug alone. It is of interest that Merrell-Dow is actively studying α-DFMO in its Strasbourg research center for the treatment of leukemia.

These papers in Volume 3 represent a fascinating account of a rapidly developing area of research whose total role in the living processes, both normal and abnormal, have yet to be elucidated. The book is highly recommended for research workers in biochemistry, medicinal chemistry, and oncology.

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Textbook of Biopharmaceutic Analysis. A Description of Methods for the Determination of Drugs in Biologic Fluids. By Robert V. Smith and James T. Stewart. Lea & Febiger, Philadelphia. 1981. xii + 308 pp. 18 × 25.5 cm. $25.00.

This book was written as a text for undergraduate and professional programs (that is, B.S. and Pharm.D.) in pharmacy, to help provide background for clinical decision making based on bioanalytical data. Its design follows the order in which an analytical problem is approached, with the parts titled "Defining the Problem", "The Separation Step", and "The Measurement Step". In the first part, two chapters deal with the types of bioanalytical problems that may be encountered, their special peculiarities, and standard reference samples. One chapter in the second part describes sample workup procedures, including solvent extraction and chromatography. The third part contains ten chapters on analytical techniques (including spectroscopy, chromatography, electroanalytical methods, immunoassay, radiochemical methods, microbiological assay, and enzyme methods), as well as statistical treatment of data.

This organization has strengths and weaknesses. The authors apparently do not expect the pharmacy student to have taken a fundamental course in analysis prior to using this text and this produces the problem that concepts and techniques that are not discussed until the third part of the book must be referred to in the first two parts. Chapter 2 on reference standards must baffle a student who does not yet know what a Beer's law plot is or how an internal standard is used. If, on the other hand, the student possessed such knowledge from an earlier course, this arrangement of material might serve very well.

The strengths of this book seem to me to be its extensive descriptions of applications of bioanalytical methods to drug problems, with citations of the original literature; the large number of figures of data, such as spectra, chromatograms, and standard curves; and the excellent structural formulas, which are numerous. Its treatment of electroanalytical methods is extensive, and its recognition of the importance of chemical reactions in analysis is unusual. The attention given to biological and biochemical methods is noteworthy.

I have some reservations, however, about the value of this book as a text; these are a result partly of its style and partly of its content. One of its peculiarities is the authors' truncation of many adjectives normally ending in *-ical* by lopping off the final syllable; thus, they write (besides the title examples) *pharmaceutic*, *graphic*, *hypothetic*, *microbiologic*, *numeric*, and *analytic*. Such an idiosyncrasy can interfere with effective communication. The

writing is often graceless. A serious drawback is the inadequacy of many explanatory passages. The book is essentially a qualitative treatment, and when a quantitative approach is attempted it is often weak. What should be a derivation tends to be a description, and some of these descriptions are mathematically or grammatically illogical. This paragraph (pp 202–203) illustrates all of these criticisms:

The decay of a radionuclide follows a first order expression for disappearance of radioactivity as indicated in Equation 1.

$$-\frac{dA}{dt} = \lambda A_0 = \ln \frac{A_0}{A} = \lambda t \quad (1)$$

Where A_0 = initial activity; A = activity at time t; t = time; λ = decay constant. By rearrangement of Equation 1, the expression described as Equation 2 can be derived.

$$A = A_0 e^{-\lambda t} \quad (2)$$

Thus, a plot of activity vs. time would be parabolically shaped and the activity would asymptotically approach the abscissa (Fig. 9-4). By understanding the definition of half-life ($t_{1/2}$) of a radioisotope (see Table 9-1), one can further define the relationship between λ and t by Equation 3.

$$\lambda = 0.693/t_{1/2} \quad (3)$$

Another example is the description of linear regression analysis (p 91), which will leave a student helpless before a set of linearly correlated data, for it nowhere suggests that a line can be drawn "by eye", but neither does it provide equations for calculating the regression parameters.

At the end of each chapter is appended a list of "Objectives" that the student should have achieved after reading the chapter. This catechism makes the book more like a trade school manual than a college textbook. Some errors that should be pointed out are Equation 10 (p 47), Equation 2 (p 81), "quantitative" instead of "qualitative" on line 2, p 65, the "equation" that isn't an equation on p 107, and the consistent misspelling "Michaelis–Menton".

As a student's first and only text in analysis this book has serious shortcomings. It can be very useful, however, as a resource to supplement a more rigorous and systematic treatment and to provide an entry to the field of modern bioanalytical practice.

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Books of Interest

Behavioral Pharmacology. Second Edition. By Susan D. Iversen and Leslie L. Iversen. Oxford University Press, London. 1981. xii + 305 pp. 15 × 22.5 cm. $10.95 paper; $17.95 cloth.

Methods of Biochemical Analysis. Volume 27. By David Glick. Wiley, New York. 1981. vii + 537 pp. 16 × 23 cm. $42.50.

Fieser and Fieser's Reagents for Organic Synthesis. Volume 9. By Mary Fieser, Rick L. Danheiser, and William P. Roush. Wiley, New York. 1981. 569 pp. 16 × 23 cm. $39.50.

Hazard in the Chemical Laboratory. 3rd Edition. By L. Bretherick. Royal Society of Chemistry, London. 1981. xxi + 567 pp. 16 × 21.5 cm. £15.00.

Pharmaceutical Dosage Forms: Tablets. Volume 2. By Herbert A. Lieberman and Leon Lachman. Marcel Dekker, New York. 1981. xiii + 508 pp. 18.5 × 26 cm. $59.75. A special student price of $24.50 is available for educators who adopt the book and place orders for five or more copies through the college or university bookshop. This offer is valid only in the U.S. and Canada.